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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/234,290	01/20/99	BURKLY L	10274/008003

HM12/0613

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EXAMINER	
UNGAR,S	

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 06/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applic...(s)
09/234,290	Burkly
Examiner	**Group Art Unit**
Ungar	1642

☒ Responsive to communication(s) filed on *Mar 23, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *25, 28, and 31-35* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *25, 28, and 31-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. The Election filed March 23, 2000 (Paper No. 9) in response to the Office Action of January 18, 2000 (Paper No. 6) is acknowledged and has been entered. Claims 25, 28 and 31-35 are pending in the application and claims 25, 28 and 31-35 have been amended. Claims 25, 28 and 31-35 are currently under prosecution.

2. The response (Paper No. 9) to the restriction requirement of January 18, 2000 has been received. Applicant has canceled and amended the claims to conform to the restriction requirement. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election, by cancellation and amendment, has been treated as an election without traverse (MPEP 818.03(a).

3. It is noted that a priority date of May 22, 1995 has been set for claims drawn to EILDV for the instant application serial number 09/234,290. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date of May 22, 1995, applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Specification

4. The specification on page 1 should be amended to reflect the status of the parent applications.

Drawings

5. The drawings are objected to because of the following informalities:

(a) Figure 5 recites PSS->Y but PSS->Y is not defined either on the figure or in the Brief Description of the drawings. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

7. Claims 25, 28 and 31-35 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for the treatment of insulin dependent (type I) diabetes comprising administering a composition comprising a soluble fibronectin polypeptide. The specification teaches that there has been little success in treating human diabetes and there is a need for immunosuppressive components for use in the prediabetic stage. It has been surprisingly discovered that administering an anti-VLA-4 antibody (which binds specifically to $alpha_4$ subunit of VLA-4) significantly reduced the incidence of diabetes in a well established NOD mouse model of diabetes, comparable to human type-I diabetes (p. 4, lines 15-25). The specification further teaches that the VLA-4 binding agents are preferably administered parenterally and provides general teachings about dosages (p. 13, lines 4-25). One cannot extrapolate the teaching of the specification to the enablement of the claims because the art of diabetes treatment is clearly not predictable or developed and

because the specification does not provide teachings to establish effective dosages or methods of administration of the claimed fibronectin polypeptides for treatment of insulin dependent (type I) diabetes and does not teach how to insure that the polypeptides interact at the proper site of action and do so at a sufficient concentration and for a sufficient period of time. Further, the specification does not provide teachings on the pharmacokinetics of the soluble fibronectin polypeptides that would provide guidance for the administration of and/or dosage of the polypeptide including parameters such as biological stability, half-life or clearance from the blood, the effects of proteolytic degradation or immunological activation, the effects of absorption of the polypeptides of the composition by fluids, cells and tissues where the polypeptide has no effect or the ability of the polypeptide of the formulation to penetrate tissues or cells where its activity is to be exerted. The specification clearly fails to provide any details about methods of administering the claimed fibronectin polypeptide, targeting the polypeptide to the appropriate cells, stability of a polypeptide *in vivo*, or appropriate doses of polypeptide of the invention to achieve the desired effect, nor does the specification provide working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed method with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the invention as claimed.

Further, as drawn specifically to claim 32, wherein the fibronectin polypeptide is joined with a toxin moiety, the specification teaches that the VLA-4

is expressed on both lymphocytes and macrophages (p. 2, lines 12-14). It is well known that binding of toxins, targeted to cell surface antigens by antigen binding moieties, leads to the killing of the cells targeted. It does not appear that the polypeptides of the invention are specific only for macrophages and lymphocytes involved in the development of diabetes. It would appear that the result of the treatment as claimed, that is with a toxin/fibronectin molecule, would result in the destruction of all lymphocytes and macrophages expressing VLA-4 which would result in a general immunosuppression of the prediabetic mammal or the mammal with partial beta cell destruction. It cannot be predicted how a general immunosuppression would treat insulin dependent (type I) diabetes, especially in a prediabetic mammal. The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed method with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the invention as claimed.

8. If Applicant were able to overcome the rejection under 35 USC 112, 1st paragraph above, Claims 25, 28 and 31-35 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of insulin dependent (type I) diabetes comprising administering a composition comprising a soluble fibronectin polypeptide which comprises an EILDV motif, does not reasonably provide enablement for a method for the treatment of insulin dependent (type I) diabetes comprising administering a composition comprising a soluble fibronectin polypeptide. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is noted that Taber's Cyclopedic Medical Dictionary, 1985, 16th Ed., F.A. Davis and Co., Philadelphia, p. 1447 defines a polypeptide as a union of two or more amino acids. Thus it is assumed for examination purposes that a fibronectin polypeptide is a polypeptide that comprises two or more consecutive amino acids of fibronectin.

The claims are drawn to a method for the treatment of insulin dependent (type I) diabetes comprising administering a composition comprising a soluble fibronectin polypeptide. This includes any fibronectin polypeptide of any length. The specification teaches that to date there has been little success in treating human diabetes and there is a need for immunosuppressive components for use in the prediabetic stage. It has been surprisingly discovered that administering an anti-VLA-4 antibody (which binds specifically to $alpha_4$ subunit of VLA-4) significantly reduced the incidence of diabetes in a well established NOD mouse model of diabetes, comparable to human type-I diabetes (p. 4, lines 15-25) and that the invention is drawn to a method for treatment of insulin dependent (type-I) diabetes in a prediabetic and in particular comprises the step of administering to the prediabetic individual a VLA-4 blocking agent in an amount effective to provide inhibition of the onset of diabetes, including fibronectin peptides containing the amino acid sequence EILDV. The agents block VLA-4 by competing with the cell-surface binding protein for VLA-4 or otherwise altering inhibiting or blocking VLA-4 function and specifically include fibronectin peptides containing the amino acid

sequence EILDV (p. 5, lines 1-20). The specification exemplifies the successful treatment of prediabetic mammals and those with partial beta cell destruction with antibodies and a VCAM-Ig fusion protein that specifically target the $alpha_4$ subunit of VLA-4 (see Examples). One cannot extrapolate the teaching of the specification to the scope of the claims because the specifically clearly reveals the unpredictable nature of the treatment of the insulin dependent type I diabetes art in revealing that to date there has been little success in treating human diabetes and that there is a need for immunosuppressive components for use in the prediabetic stage. The specification clearly exemplifies that administration of effective amounts of agents that specifically target the $alpha_4$ subunit of VLA-4 are successful in the treatment of diabetes and teach that agents of the invention include fibronectin peptides that contain the EILDV amino acid sequence. The specification does not teach how to use fibronectin polypeptides other than a polypeptide containing the EILDV amino acid sequence. It cannot be predicted from the information in the specification or in the art that any fibronectin polypeptide, for example one that consists of two amino acid residues or one that does not contain the EILDV amino acid sequence will function as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to use the claimed fibronectin polypeptide with a reasonable expectation of success in the claimed method. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

9. If Applicant were able to overcome the rejections under 35 USC 112, 1st paragraph above, Claims 31 and 32 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising a fibronectin polypeptide and a toxin moiety, does not reasonably provide enablement for a fibronectin polypeptide that is a component of a chimeric molecule or said chimeric molecule wherein the chimeric molecule further comprises a toxin moiety. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to chimeric molecules. This includes a whole universe of undefined molecules. The specification teaches that the invention features a chimeric molecule which includes a VLA-4 targeting moiety, optionally a second peptide and a toxin moiety (p. 9, lines 26-36) and the specification teaches the production of a VCAM-Ig fusion protein (p. 23). One cannot extrapolate the teaching of the specification to the scope of the claims because the specification provides no guidance on the production of a chimeric molecule other than a VCAM-Ig fusion protein and provides no guidance on what the "optionally second peptide" might be. There is no guidance in the specification for the production of other types of fusion proteins which would fall into the category of "chimeric" molecules. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the

protein. Burgess et al. J of Cell Bio. 111:2129-2138, 1990. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Lazar et al. Molecular and Cellular Biology 8:1247-1252 (1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. It is clear that modification of the fibronectin polypeptide in the production of a "chimeric molecule" would require addition of amino acids and it could not be predicted what affects these additional residues would have on the specificity and function of the fibronectin polypeptide. Certainly it would be expected that three dimensional conformation changes in the polypeptide would occur and it could not be predicted from the specification whether all types of "chimeric" molecules would retain the ability to function as claimed. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

10. Claims 31 and 32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31 and 32 are indefinite in the recitation of "chimeric molecule" because the exact meaning of the word chimeric is not known. The term chimeric is generic to a class of molecules which are products of genetic shuffling of several other active proteins. The term encompasses soluble fibronectin polypeptides fused

to other proteins as well as soluble fibronectin polypeptides wherein any domain of the polypeptide is substituted by corresponding regions from other VLA-4 blocking agents.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 8, 2000